RESEARCH

Nasal oxytocin administration does not influence eye gaze or perceived relationship of male volunteers with physicians in a simulated online consultation: a randomized, placebo-controlled trial

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Abstract

The patient–physician relationship is a critical determinant of patient health outcomes. Verbal and non-verbal communication, such as eye gaze, are vital aspects of this bond. Neurobiological studies indicate that oxytocin may serve as a link between increased eye gaze and social bonding. Therefore, oxytocin signaling could serve as a key factor influencing eye gaze as well as the patient–physician relationship. We aimed to test the effects of oxytocin on gaze to the eyes of the physician and the patient–physician relationship by conducting a randomized placebo-controlled crossover trial in healthy volunteers with intranasally administered oxytocin (with a previously effective single dose of 24 IU, EudraCT number 2018-004081-34). The eye gaze of 68 male volunteers was studied using eye tracking during a simulated video call consultation with a physician, who provided information about vaccination against the human papillomavirus. Relationship outcomes, including trust, satisfaction, and perceived physician communication style, were measured using questionnaires and corrected for possible confounds (social anxiety and attachment orientation). Additional secondary outcome measures for the effect of oxytocin were recall of information and pupil diameter and exploratory outcomes included mood and anxiety measures. Oxytocin did not affect the eye-tracking parameters of volunteers' gaze toward the eyes of the physician. Moreover, oxytocin did not affect the parameters of bonding between volunteers and the physician nor other secondary and exploratory outcomes in this setting. Bayesian hypothesis testing provided evidence for the absence of effects. These results contradict the notion that oxytocin affects eye gaze patterns or bonding.

Key Words

- oxytocin
- crossover trial
- eye gaze
- eye-tracking
- patient–physician relationship

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Introduction

The patient–physician relationship is critical for patients' health. For example, optimal trust and therapeutic alliance positively affect patients' psychological well-being, adherence to medication, and treatment response (1, 2) and can even influence their healthcare use and intention to vaccinate (3, 4). Therefore, improving patient–physician relationships has the potential to positively affect healthcare at large. Consequently, it is worthwhile to investigate the underlying mechanisms of *how* patients and physicians bond, from both a psychological and a neurobiological perspective.

Verbal and non-verbal communication is a crucial constituent of patient–physician relationships (5). Verbal communication encompasses, for instance, the content or amount of information that is shared (5). Non-verbal communication, such as body language, also contributes to the patient–physician relationship (5). A salient aspect of non-verbal communication is the degree of eye contact between patient and physician (6). Through eye contact, the physician enters a critical first stage of social engagement with the patient (6). Eye contact can be defined as a mutual gaze toward the eye region of others (7). Gaze toward the eyes ('eye gaze') regulates several aspects of communication, such as turn-taking in conversation (8). Furthermore, eye gaze transmits social and attentional information (9, 10), both of which are important elements in patient–physician communication and may therefore affect the quality of the relationship. Sub-optimal levels of eye gaze between physicians and patients can negatively affect patient–physician relationships, including the reduced trust of patients in their physicians (6, 11). Similarly, a higher degree of mutual eye gaze leads to higher levels of patient trust in their physician (12).

The neurological basis for gaze toward the eyes is often studied as an integral part of the processing of faces. Neuroimaging studies show that activity in specific brain areas, such as the amygdala or the fusiform face area, underlie face processing (13, 14, 15). Several studies have linked the neuropeptide oxytocin to the processing of facial stimuli, especially of eye gaze (13, 14). Therefore, oxytocin may serve as an underlying neurobiological mediator directing eye gaze (16, 17, 18) and the patient–physician relationship (19).

Oxytocin is a nine-amino acid neuropeptide influencing human attachment and social behavior (20). Oxytocin functions both as a neurotransmitter and as a hormone. Intranasally administered oxytocin has been used to investigate the effects of oxytocin on social cognition and behavior in humans (21) as it increases oxytocin concentrations in the central nervous system (22). Studies show, for example, that oxytocin administration improves people's recognition of facial emotional expressions (23) and increases their sensitivity to socially salient cues (24). Such effects of oxytocin have been explained by the social salience hypothesis, which posits that the effects of oxytocin on various social behaviors are dependent both on contextual social cues (such as a competitive or a cooperative environment) and on baseline individual differences such as personality traits or degrees of psychopathology (25). According to the social salience hypothesis of oxytocin, oxytocin increases the salience or noticeability of social cues, influencing cognitive processes and behaviors that depend on this information. The social salience hypothesis of oxytocin also proposes that by increasing the salience of social cues, visual attention is drawn to socially relevant stimuli, like the eye region (21). Therefore, it is expected that oxytocin administration increases gaze toward the eyes in socially salient stimuli. Some studies examining the effects of intranasally administered oxytocin have indeed shown increased gaze toward the eye region (13, 16, 17, 18, 26). In contrast, other studies reported no effects of oxytocin administration on gaze toward the eye region (27). Many of the previously mentioned studies researching the effect of oxytocin on eye gaze and relational outcomes have been statistically underpowered (28), which reduces the chances of detecting a wide range of effect sizes. Therefore, more substantial evidence is needed for the effects of oxytocin on eye gaze, using study designs that can reliably detect a wider range of effect sizes (28).

We aimed to examine the relation between oxytocin, eye gaze, and the physician–patient relationship. Specifically, we aimed to assess whether oxytocin administration increased the level of eye gaze toward the eye area of a physician and the patient–physician relationship in a simulated online consultation. Online consultations are generally well accepted by patients from different age groups and with different health conditions since it simulates in-person, face-to-face consultation (29). To that end, we designed a pre-registered, placebo-controlled, randomized experiment, in which we compared the effects of intranasal administration of oxytocin and placebo on the gaze of healthy volunteers toward the eye region of a physician. We expected oxytocin to increase the gaze toward the eye region. In addition, we compared the effects of oxytocin and placebo on the

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physician–patient relationship (primarily on the levels of trust in the physician and secondarily satisfaction with the physician and perception of physician communication style), which is of fundamental importance for health-related outcomes such as medication adherence (30), and expected oxytocin to improve the relationship. Other secondary outcome measures were recall of information, because of its importance in medical care (31, 32), and pupil diameter, which has previously been shown to dilate in response to oxytocin (21). In sum, previous research studied the relation between the primary and secondary outcome measures before, albeit with inconsistent results. Exploratory outcomes for the effect of oxytocin included measures of mood and state anxiety. Social anxiety and attachment orientation were also included as possible confound variables (33).

Methods

Volunteers

Ninety-eight volunteers from the general and student community were recruited through online and paper pamphlets. Volunteers had to be aged between 18 and 35 years and speak sufficient Dutch for participation. They were instructed to refrain from alcohol, smoking, caffeine, and drug use 24 h before the experiment and from food, drinks (except water), as well as intensive exercise 2 h before the experiment (34). Volunteers were excluded if they reported a hypersensitivity to oxytocin or to any of the excipients of oxytocin or the placebo spray formulations. Females were excluded to rule out possible confounding effects of sex-specific oxytocin activity and therefore a potential heterogeneous response (35).

The study was pre-registered at ClinicalTrialsRegister.eu (number 2018-004081-34) and approved by the Medical Ethical Committee of the AMC (NL69901.018.19). All experimental procedures were performed in accordance with relevant guidelines and regulations of the medical research ethics committee of the Amsterdam Medical Centre, following the Declaration of Helsinki. All participants provided written informed consent.

Study design

We conducted a randomized crossover trial with 24 IU intranasally administered oxytocin (Syntocinon 40 IU/mL, Alfasigma S.p.A., Bologna, Italy) (one puff of 12 IU per nostril) as the intervention and, on another occasion, a placebo (with similar ingredients as the oxytocin solution, such as chlorobutannol, but without the active ingredient; one puff per nostril) as the control condition. The dose was determined based on previous studies reporting statistically significant results on gaze (16, 17, 18). Both researchers and volunteers were blinded with respect to the intervention. The sequence of oxytocin and placebo administration was determined by the balanced assignment. Volunteers visited the lab twice with a washout period of exactly 7 days and at precisely the same time of the day, to account for possible variations in circadian oxytocin levels (36). Volunteers engaged in a simulated Skype consultation with the physician. We used eye-tracking hardware to assess volunteers' gaze toward the physician on the video and to assess pupil size (as a possible indicator of trust (37)) and questionnaires to assess self-reported outcome measures. The study lab consisted of two adjacent rooms, one for the researcher (including the control of the hardware and software) and one for the volunteers (with only artificial lighting to improve eye-tracking data quality).

Procedure

Figure 1 illustrates a graphical representation of the procedures. Upon arrival at the lab, the participants provided written informed consent and were screened for the study inclusion criteria. Instructions provided by the researchers to the participants are documented in Appendix A (see section on supplementary materials given at the end of this article). Volunteers first completed baseline questionnaires assessing sociodemographic and background characteristics. Subsequently, the researcher administered the medication or placebo intranasally, randomized by the local pharmacy. Medication was administered using the Intranasal Mucosal Atomization Device, which was previously successfully used with oxytocin (38). This device atomizes the nasal medication into a fine mist of particles 30–100 microns in size, which is the optimal size for absorption across mucosal membranes into the bloodstream avoiding first-pass metabolism (39). The device has a soft conical plug on the tip that forms a seal with the nostril, preventing the expulsion of fluid. During the administration, researchers followed the guidelines of the nasal device manufacturer, in combination with the standardized recommendations of Guastella and colleagues (40). Intranasal administration was followed by a wait time of 40 min, during which volunteers had access to magazines depicting neutral images of nature or architecture.

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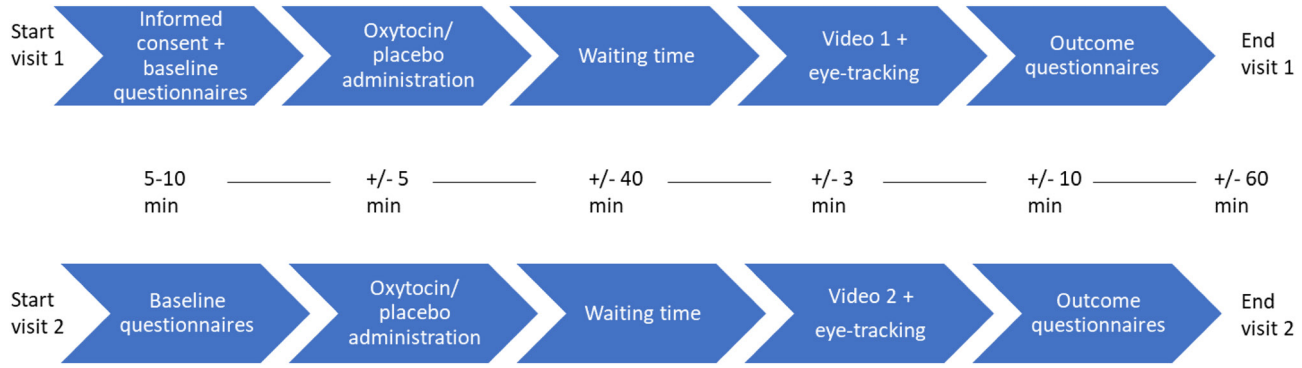

Figure 1
Graphical illustration of the procedure and timeline of the experiment.

This waiting time was based on earlier studies (16, 17, 18, 27, 41). For the primary experimental task, volunteers were informed they would have an interaction with a physician about human papillomavirus (HPV) vaccination. Subsequently, they participated in a standardized, simulated Skype call (similar to previous research (42)) depicting a real physician who directly addressed them, creating the illusion of a real-time online interaction. The Skype call had been video-recorded using a webcam to enhance realism. The physician gazed as much as possible into the webcam, establishing a direct gaze toward the participant. Figure 2 shows an illustration of this task. During this simulated video call, the physician provided arguments in favor of and against the vaccination of males to prevent HPV infection. This topic was likely to be engaging to the study population because of its relevance to society and to their own health (43). While participating in the experiment, gaze and pupil size of the participants were tracked. They rested their head on a chin and forehead rest to enhance stability and ensure the quality of measurement. After the simulated video call, participants completed a second questionnaire assessing primary, secondary, and exploratory outcome measures. During the second study visit, 7 days later, a second simulated video call was shown, including different pros and cons of HPV vaccination. Appendix B documents the arguments for HPV vaccination of both sessions with equivalent characteristics. The order of the two videos was randomly counterbalanced to exclude learning effects.

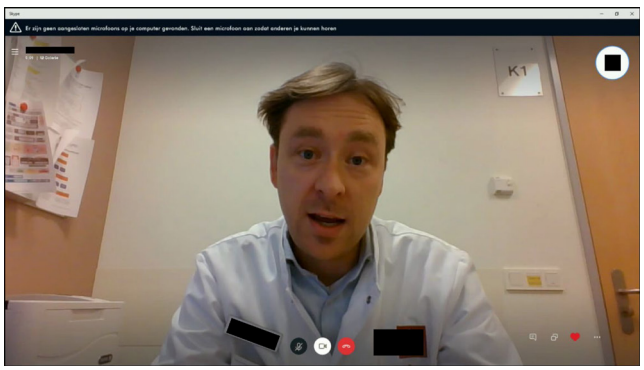

Figure 2
Screenshot depicting the Skype call setup. Note: Written informed consent for publication of the displayed physician was obtained.

Questionnaires

To assess the outcomes of our trial on patient–physician relationships, we used three validated questionnaires. Our primary relationship outcome questionnaire was volunteers' trust in the physician, assessed using the Wake Forest Physician Trust Scale (44). We omitted one item that was not applicable to our communication process (referring to the listening capabilities of the physician). The questionnaire consisted of nine items, answered on a 5-point Likert scale ('completely disagree' to 'completely agree'), where higher scores indicated stronger trust in the physician. Our sample had a Cronbach's alpha of 0.84.

We included secondary outcome questionnaires to evaluate the patient–physician relationship in our trial. We assessed self-reported satisfaction of the participants with the physician, using one visual analog scale ranging from 0 (not likely at all) to 100 (most likely) stating: 'I would recommend this doctor to a friend or family member'. Higher scores indicated higher satisfaction with the physician. We additionally assessed volunteers' perception of physicians' communication style, using the validated 17 Physicians' Communication Style items (translated to Dutch for this study with forward-backward translation) on two subscales: 12 items for affiliativeness

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and 5 items for dominance/activity (45). Three items of the original scale were deleted that were not applicable to our setting. Items are answered on a 5-point Likert scale ('strongly disagree' to 'strongly agree'); high scores were indicative of the physician's communication style being perceived as more affiliative or dominant. The Cronbach's alpha of our sample was 0.81.

For information recall, we assessed both free recall and recognition of the information regarding HPV vaccination provided in the videos, using five self-developed items. The free recall items were open-ended questions, such as 'The physician has just told you that a type of cancer caused by HPV is on the rise at the moment. What kind of cancer is this?' and the recognition items were the open-ended questions with multiple choice answers. Volunteers received 0 (incorrect), 0.5 (partially correct), or 1 (correct) point per question. Higher scores were indicative of higher information recall. Two authors manually double-scored all answers and resolved discrepancies through discussion with two additional authors.

We also measured changes in mood and state anxiety as exploratory outcome measures of the effect of oxytocin. We measured change in mood (i.e. positive and negative affect), using the 20-item Positive And Negative Affect Schedule (PANAS) before and after the consultation (46). Items (e.g. I feel 'Interested' (positive affect) or I feel 'nervous' (negative affect)) are answered on a 5-point Likert scale (from 1 'not or hardly' to 5 'very strongly'). Higher scores on the subscales indicated higher positive or negative affect. Our study sample recorded a Cronbach's alpha of 0.74.

Change in state anxiety was assessed using the 6-item short form of the Spielberger State-Trait Anxiety Inventory, state scale before and after the consultation (47). This measured the volunteers' anxiety at the given moment (e.g. 'I feel tense'), answered on a 4-point Likert scale (1 being 'not at all' to 4 being 'very much'), and higher scores indicated a greater change in anxiety. Cronbach's alpha was acceptable, at 0.68.

We assessed the perceived realism of the participants in the task, using one visual analog scale ranging from 0 (not at all) to 100 (completely) stating: 'To what extent did you feel you were talking to the doctor, despite the limitations of Skype and the chin rest?'. Higher scores indicated higher perceived realism.

We addressed trait measures by including questionnaires on individual levels of social anxiety and attachment orientation. Social anxiety was measured with the six-item Social Interaction Anxiety Scale and six-item Social Phobia Scale (SIAS-6, SPS-6) (48). The questionnaire comprised 12 items in total (e.g. 'I find it difficult to look at other people'), answered on a 5-point Likert scale (from 1 'does not apply to 5 'completely applicable'). Higher scores were indicative of greater social anxiety. Our sample yielded a Cronbach's alpha of 0.86.

Attachment orientation was measured with the Experiences in Close Relationship Scale-Short Form (ECRS-SF), which scores on two dimensions: attachment avoidance and attachment anxiety (49). This questionnaire consisted of 12 items (e.g. 'I usually discuss my problems and concerns with my partner') answered on a 7-point Likert scale (1 'totally disagree' to 7 'totally agree'). Higher scores indicated higher attachment avoidance or anxiety. Cronbach's alpha was 0.71 in our sample.

Eye tracking

We used an SMI-RED 500 screen eye-tracker (SensoMotoric Instruments; retailed by iMotions, A/S, Copenhagen, Denmark) complemented with a head and chin rest to capture our primary eye gaze outcome. The distance between the eye tracker and the eyes was held stable at 70 cm, across all visits. Furthermore, the eye-tracking room contained solely artificial lighting, which was stable across all conditions. We calibrated the eyes of the participants in the SMI Experiment software. We used a 5-point calibration method, which evaluates the measurement accuracy of the gaze coordinates for five fixed points spread across all parts of the screen following the iView X system manual.

The eye tracker was also used to measure pupillometry, a non-invasive method of measuring pupil diameter over time. The pupil data were recorded in millimeters for both eyes, as a direct effect of oxytocin on pupil dilation and a possible indicator of trust (37). For gaze location and for pupil diameter, we exported the raw eye-tracking data (meaning that no filters, such as a fixation filter, were used given that there is no standard for fixation detection (50)) using SMI Experiment Center Be-Gaze.

Data preparation

For the gaze toward the eye region, we exported raw eye-tracking data for every participant using the gaze location based on both eyes. To calculate the amount of volunteer gaze toward the eye region of the physician as area of

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interest, we used a validated face recognition algorithm (51). For an elaborate description of the analysis see Appendix C. Results were exported to SPSS for Windows, version 24.0 (IBM Corp.) to calculate percentages of gaze location, since we previously found that this was the most suitable gaze measure, which related to patient trust in a real-life patient–physician interaction (30, 52).

For the pupillometry analysis, we first pre-processed the raw data to remove blinks and artifacts (53). We excluded both pupil diameters when the value of either the left or the right eye was missing (median = 3.30% of time, range =.30–14.21%). Then, we calculated mean pupil diameter by averaging over time of the stimulus (21).

To assess eye-tracking data quality, we exported the accuracy for both eyes from the eye-tracking software. We used a cutoff of 2.0° for either the right or left eye. Second, we controlled for the total summed amount of data loss and used a cutoff of 20% of data loss. Third, we calculated the data precision, root mean squared (RMS) as a measure for deviation, for both eyes in MATLAB R2020b (The MathWorks, Inc., Natick, MA, USA) using a precision cutoff of 1.0° for both eyes.

Statistical analysis

We planned to include 76 healthy young male volunteers, to enable detecting an effect size of 0.33. This is conventionally considered as a medium-to-small effect (54). Previous comparable studies found effect sizes ranging from 0.35 to 1.2 (16, 17, 18), but given the risks of effect size inflation in published studies (55), we powered our study to detect a smaller effect size, two-tailed α of 0.05, with 80% statistical power.

Data cleaning was done in SPSS for Windows, version 24.0 (SPSS Inc. 26 ed., 2020). We excluded missing data listwise and specified the number of missing data. Hypothesis testing was done using the R statistical programming language (R Development Core Team, Vienna, Austria) with a priori defined two-tailed α-value of 0.05 for all frequentist tests. R scripts are available following this link: https://osf.io/2b4z8/. Because of the within-subject design and the use of ordinal data, we conducted a Wilcoxon signed-rank test for differences in treatment (control vs treatment) and reported the effect sizes by rank biserial correlation (rrb) (R function: wilcox.test, package: stats, and rank_biserial, package: effectsize) (56). Furthermore, we ran a Baron and Kenny mediation analysis to test whether the level of eye gaze mediated the effect of oxytocin on trust (R function: lm, package: stats) (57), which consists of a set of paired sample *t*-tests and a multiple regression. We repeated the same analysis with our secondary outcome measures (satisfaction with physician, physician communication style (affiliativeness and dominance), recall of information (free recall and recognition), and pupil diameter) and exploratory outcome measures (change in positive mood, negative mood, and state anxiety). Finally, to investigate any influence of participant characteristics, we correlated age, education level, and attachment style, to the difference scores of the main outcomes, gaze and trust, by subtracting the value of the placebo visit from the oxytocin visit (R function: cor, package: stats). We used the Pearson's correlation (r) to calculate the correlations between two continuous variables, the point-biserial correlations (r_{pb}) to calculate the correlation between a continuous and a categorical variable, and the Spearman's rank order correlation (ρ) was used to calculate the correlation between two ranked variables.

In addition to frequentist analyses, we also used Bayesian hypothesis testing for the Wilcoxon signed-rank tests in JASP (58). Bayesian inference can be used to assess the relative evidence of a null model to an alternative model (59). Therefore, Bayesian models were used to complement the regression and mediation analyses to examine the relative strength of evidence for both the null and the alternative hypotheses using a Cauchy distribution as a prior with a width parameter of 0.71, given our non-directional hypothesis (60). A Bayes factor (BF_{10}) value less than 0.33 suggests that the null model is more than three times more favored than the alternative model, given the data. A BF_{10} over 3 suggests that the alternative model is more than three times more favored than the null model, given the data.

Results

Descriptives

We included 68 volunteers in the final analyses. Figure 3 provides the details of the CONSORT flow diagram, which includes reasons for dropout and data exclusion, and Table 1 provides the sociodemographic and psychological characteristics of the sample. The median age of the participants was 22 years (range 18–33 years). The quality of the eye-tracking data in our sample was as follows: median accuracy degrees of 0.47 for the *X* axis and 0.41 for the *Y* axis (range = 0.010–1.31),

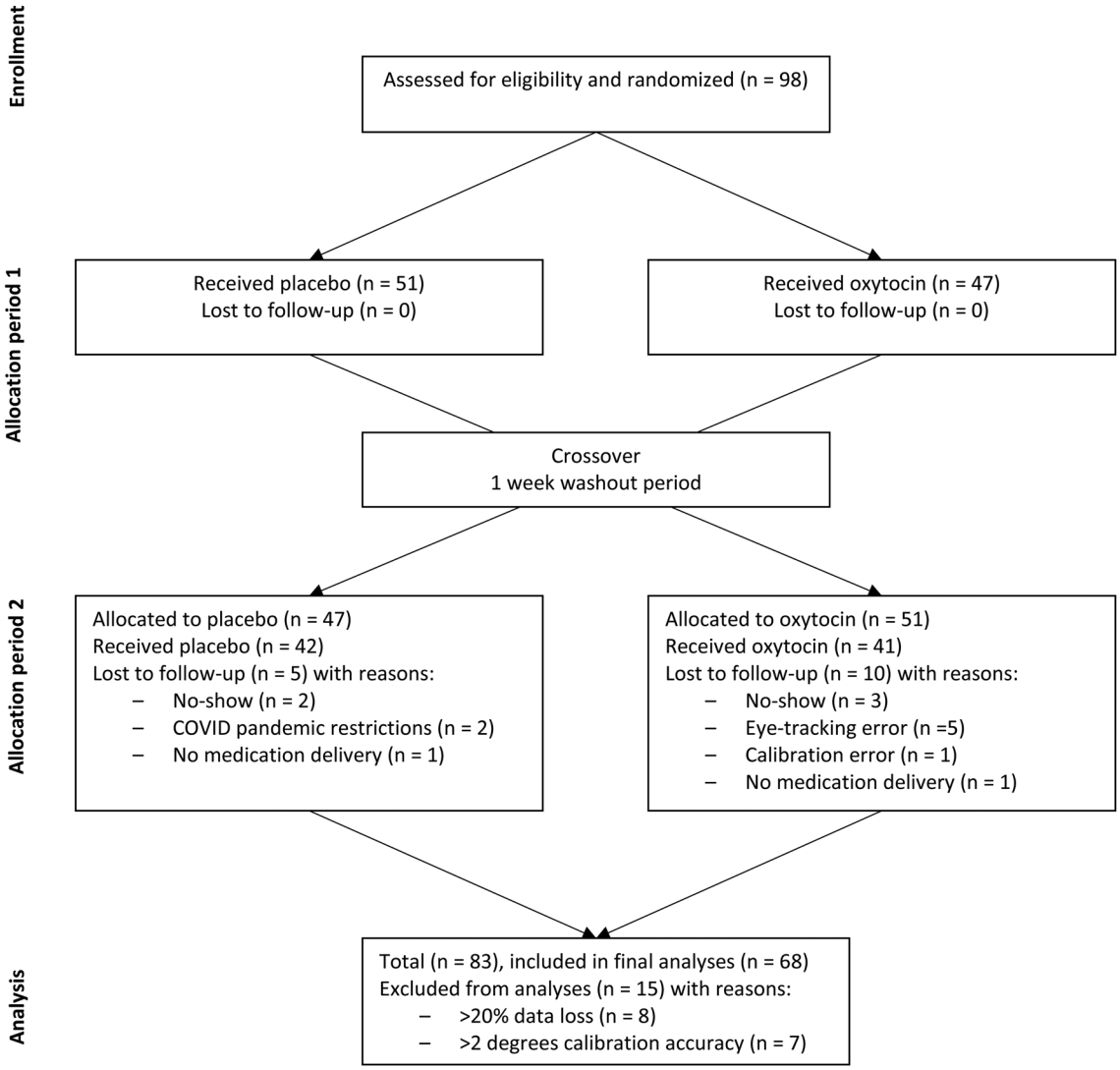

Figure 3
CONSORT flow diagram.

a median precision of 0.04 RMS degrees for the *X* and *Y* axes (range = 0.02–0.73), and a median of 3.38% of data loss (range = 0.29–18.49). Table 1 provides descriptive statistics for gaze toward the eyes, trust in physician, satisfaction with physician, physician affiliativeness, physician dominance, recall of information, recognition of information, and pupil size and exploratory measures (change in positive mood, negative mood, and anxiety) per condition. The perceived realism of the participants in the task was 40 (range: 0–89) over both visits.

Effects of oxytocin on gaze to the eyes and trust

Oxytocin did not affect gaze toward the eye region as indicated by our rank biserial correlation of rrb = 0.10 $P = 0.40$ (Table 2, Fig. 4). Furthermore, oxytocin did not significantly affect trust in the physician as indicated by our rank biserial correlation of rrb = 0.02, $P = 0.91$.

Bayesian hypothesis tests were consistent with the frequentist analyses. The Bayes factor for the gaze toward the eyes model was 0.16, suggesting 6.2 times more evidence for a null model relative to an alternative model. Therefore, the data suggest that it is unlikely that oxytocin had an effect on gaze toward the eyes. Similarly, the Bayes factor for trust in the physician is 0.13, suggesting that the null model is 7.5 times more likely than the alternative hypothesis. Therefore, it is unlikely that oxytocin had an effect on trust in the physician either.

Furthermore, the level of gaze toward the eyes did not mediate the effect of oxytocin on trust, as indicated

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Table 1 Sociodemographic and psychological characteristics of our sample.

Sociodemographic or psychological characteristic	Value
Self-identified nationality (*N* (%))	
Dutch	63 (92.6%)
Other European nationalities	1 (1.5%)
South American	1 (1.5%)
Middle East	2 (2.9%)
Other (not specified)	1 (1.5%)
Education level (*N* (%))	
None/primary school	1 (1.5%)
Secondary/lower-level vocational school	44 (64.7%)
College/university	23 (33.8%)
Social anxiety (MDN (range)) (SIAS-6 SPS-6)	4 (0–29)
Avoidant attachment orientation (MDN (range)) (ECRS-SF)	18 (9–34)
Anxious attachment orientation (MDN (range)) (ECRS-SF)	8 (8–29)

by the non-significant multiple regression (b: $\beta = 0.00$, $P = 0.88$) of the Baron and Kenny mediation analysis, shown in Fig. 5. Also, all tests that comprise the Baron and Kenny mediation analysis were non-significant. This means that oxytocin did not relate to trust in the physician (c) ($t(67) = 0.25$, $P = 0.80$) and gaze toward the eyes did not relate to trust in the physician (a) ($t(67) = 0.76$, $P = 0.45$), as shown by the paired sample *t*-tests. Moreover, gaze toward the eyes did not relate to trust in the physician when corrected for the effect of oxytocin on trust in the physician (c') ($\beta = 0.00$, $P = 0.36$), as shown by the multiple regression.

Effect of oxytocin on secondary outcome measures

Oxytocin did not affect our secondary outcome measures as indicated by our rank biserial correlations. There was no significant association between oxytocin and satisfaction with the physician (rrb = 0.05, $P = 0.71$, $BF_{10} = 0.21$), physician affiliativeness (rrb = 0.07, $P = 0.51$, $BF_{10} = 0.20$), physician dominance (rrb = 0.09, $P = 0.48$, $BF_{10} = 0.30$), free recall of information (rrb = 0.17, $P = 0.17$, $BF_{10} = 0.90$), information recognition (rrb = 0.18, $P = 0.23$, $BF_{10} = 0.38$), or pupil diameter (rrb = 0.09, $P = 0.49$, $BF_{10} = 0.17$). Furthermore, there was no effect of oxytocin

Table 2 Descriptive statistics for all outcome measures per condition.

	Oxytocin		Placebo		Difference/test	
	Mean (s.d.)	Median (IQR)	Mean (s.d.)	Median (IQR)	Rank biserial correlation (*P*)	*Z* statistic
Primary outcome measures *(n)*						
Gaze toward the eye region, % of time (68)	29.9 (18.0)	25.3 (28.4)	31.5 (19.9)	29.9 (30.9)	0.07 (0.60)	−0.53
Trust in the physician, WFPTS, range=1–5 (68)	3.8 (0.6)	3.7 (0.9)	3.8 (0.7)	3.8 (1)	−0.01 (0.86)	−0.08
Secondary outcome measures *(n)*						
Satisfaction with physician, range = 0–100 (64)	60.5 (23.1)	67.0 (26)	61.9 (22.4)	67 (26.8)	0.18 (0.23)	−1.19
Physicians' communication style – affiliativeness, range = 0–60 (68)	42.8 (6.6)	44.0 (7)	42.3 (6.2)	43.5 (7)	−0.14 (.34)	−0.96
Physician's communication style – dominance/activity, range = 0–25 (68)	9.3 (2.9)	9.0 (4)	9.7 (2.7)	9.0 (3)	0.18 (0.25)	−1.16
Free recall of information, range = 0–5 (68)	3.7 (1.0)	4.0 (1.5)	3.4 (1.1)	3.5 (1.5)	−0.25 (0.09)	−1.69
Recognition of information, range = 0–5 (68)	4.0 (0.9)	4.0 (1)	3.7 (0.9)	4.0 (1)	−0.21 (0.19)	−1.30
Pupil diameter, in millimeters (60)	4.3 (0.5)	4.3 (0.6)	4.3 (0.5)	4.2 (0.7)	−0.06 (0.70)	−0.39
Exploratory measures *(n)*						
Change in positive affect, PANAS (67)	−1.3 (4.3)	−1.0 (4.5)	−1.4 (4.6)	−1.0 (5.3)	0.00 (1.00)	0.00
Change in negative affect, PANAS (67)	−0.8 (2.6)	−1.0 (2)	−1.0 (2.6)	−1.0 (3)	−0.13 (0.38)	−0.89
Change in state anxiety (STAI-S) (67)	−0.6 (2.2)	0.0 (3)	−0.5 (2.3)	0.0 (2.3)	−0.02 (0.91)	−0.12

IQR, interquartile range; PANAS, Positive And Negative Affect Scale; s.d., standard deviation; STAI-S, State-Trait Anxiety Inventory – State; WFPTS, Wake Forest Physician Trust Scale.

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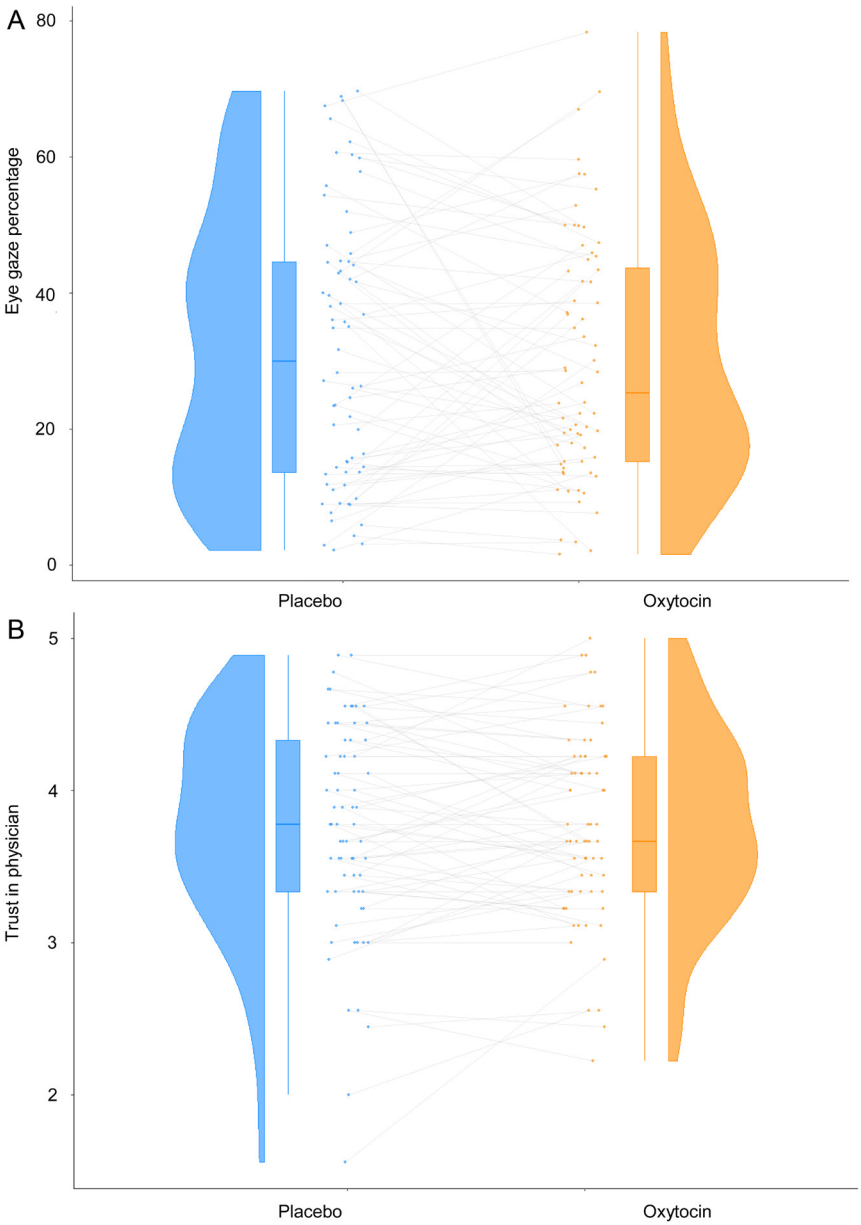

Figure 4
Raincloud plot distributions of primary outcomes. Panel A illustrates a comparison of oxytocin and placebo's effects on eye gaze percentage. Panel B illustrates a comparison of oxytocin and placebo's effects on trust in physician. Note: The raincloud plot combines an illustration of data distribution (the 'cloud') with jittered raw data (the 'rain'). All individual data points of the participants are connected through a trace line and the raincloud plots are supplemented with boxplots.

on our exploratory outcome measures, that is, change in positive affect (rrb = 0.02, P = 0.91, BF_{10} = 0.14), negative affect (rrb = 0.10, P = 0.43, BF_{10} = 0.21), and anxiety (rrb = 0.03, P = 0.89, BF_{10} = 0.14).

Correlations between participant characteristics and the effect of oxytocin

Age, education, attachment anxiety, and avoidance all had weak correlations with the difference scores of gaze (r = –0.06, P = 0.63; r_{pb} = 0.12, p = 0.33; ρ = –0.02, P = 0.88; and ρ = –0.15, P = 0.23, respectively) and trust (r = –0.06, P = 0.64; r_{pb} = 0.11, P = 0.37; ρ = 0.02, P = 0.84; and ρ = –0.10, P = 0.40, respectively).

Discussion

We tested the effects of oxytocin administration on participants' gaze toward a physician's eye region and on patient–physician relationships in a double-blind randomized crossover trial. Sixty-eight healthy men were eye tracked during a standardized simulated video call with a physician. Oxytocin did not increase gaze toward the eye region nor increased trust in the physician in this setting. Oxytocin did not affect other indicators of patient–physician relationships. Similarly, secondary analyses indicated that oxytocin did not influence recall and recognition of information by the participants or pupil diameter. Lastly, there were no effects of oxytocin

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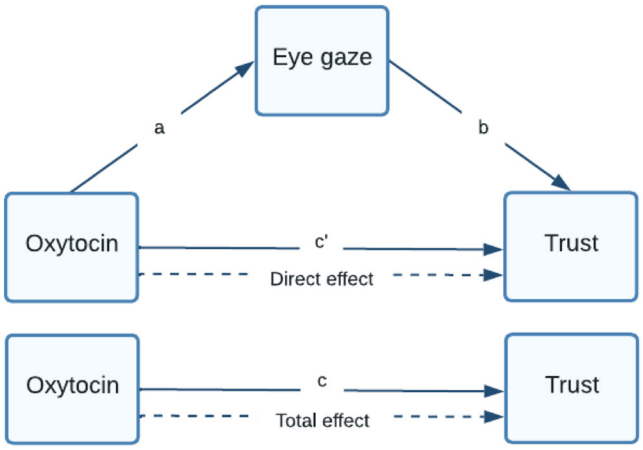

Figure 5
Schematic representation of the Baron and Kenny mediation analysis of the level of eye gaze mediated for the effect of oxytocin on trust.

administration on mood and anxiety. In sum, a single dose of oxytocin administration did not affect any of our outcome parameters.

Whereas previous studies reported that intranasal oxytocin administration increased the gaze toward the eye region, we found no effects of oxytocin on the gaze toward the eye region of the physician (16, 17, 26). Methodological differences might explain this discrepancy. Previous studies used static images as facial stimuli; instead, we used a dynamic standardized video call (17, 26). In accordance with our results, Lischke and colleagues (27) found no effects of oxytocin on gaze toward the eye region on dynamic facial stimuli. These authors (27) argued that this absence of an effect could be explained by the presentation time of their facial stimuli, which was much longer compared to previously used static facial images. However, this view is contested by findings that oxytocin increased people's gaze to another person's eye region in an interview setting, lasting approximately 5 min (16). To study gaze to the eye region, they calculated the transformed mean eye-fixation difference per second (16). In comparison, we assessed the percentage of time (7, 30) participants gazed toward the eye region in a larger experimental group and did not replicate these effects. Oxytocin may influence task-related outcomes such as increased gaze toward the eye region on pictures or while answering to a semi-structured interview (16, 18). Furthermore, oxytocin may be related to moment-to-moment effects such as eye fixation per second. However, a longer-duration stimulus, like our video consultation, better represents real-world social behavior. Therefore, it may be that oxytocin has no meaningful role in longer interactions without specific task instructions. This is also suggested in a recent longitudinal trial in which nasal administration of oxytocin did not improve the social interaction of young participants with autism spectrum disorder (61). Future research may analyze specific aspects of gaze, such as time to first fixation to the eye region or fixation patterns (62).

Similarly, we found no effects of oxytocin on the patient–physician relationship, such as trust in the physician. Previous studies reporting effects on relational outcomes such as trust used economic games to measure trust (33, 41): how much money participants were willing to transfer to another participant (the trustee). Moreover, these studies have not been reliably replicated (33, 63). Trust in the physician is a multidimensional construct (44). Therefore, a single item may not accurately index the patient–physician relationship. Alternatively, a brief video call may not have been sufficient to establish a baseline level of rapport between the participant and the physician. Indeed, previous research has demonstrated that oxytocin administration may only influence the perception of stimuli only if they are considered to be sufficiently relevant by the individual (64). Therefore, before concluding that oxytocin does not affect patient trust, future research could assess the effects of oxytocin on patients' relationship with their own physician.

Our study has some limitations. First, we did not include female participants, to rule out possible confounding effects of sex-specific oxytocin activity and therefore reduce heterogeneity in responses (35). Therefore, our results are not generalizable to females, in whom opposite effects of intranasal oxytocin have sometimes been reported (65). Second, while we designed our study to detect a medium effect size, it is possible that the effects of oxytocin on gaze toward the eye region and trust are smaller and, therefore, require an even larger sample size to reliably detect effects. Third, we administered 24 IU with an intranasal mucosal atomization device, which has previously been used to document the effects of oxytocin on eye gaze (16, 17, 18, 38). Therefore, we chose for this dose. However, without a comparison with other dosages, it is unclear whether the absence of effects of oxytocin would have been different with a higher or lower oxytocin dose. Finally, even though online consultations are increasingly common (29), the simulation video call with volunteers in our study may limit the validity of our findings (66) since it does not necessarily represent a face-to-face patient–physician interaction.

Increased trust and eye gaze were among the first reported responses to intranasal oxytocin administration (17, 41). However, in our simulated online consultation,

we found no effects of 24 IU intranasal oxytocin administration on gaze toward the eye region or on trust within the context of the patient–physician relationship, using a larger sample size and a within-subject design compared to these original reports. To advance oxytocin research, prevailing hypotheses need to be tested using approaches that facilitate hypothesis falsification (67). In conclusion, by complementing conventional frequentist hypothesis testing with Bayesian hypothesis testing, we were able to provide strong relative evidence for our null models.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-22-0377.

Declaration of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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